UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/829,504	04/21/2004	David Epstein	23239-558A (ARC-58A)	7640

30623 7590 10/17/2007

MINTZ, LEVIN, COHN, FERRIS, GLOVSKY
AND POPEO, P.C.
ONE FINANCIAL CENTER
BOSTON, MA 02111

EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
10/17/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/829,504	EPSTEIN ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-63* is/are pending in the application.

4a) Of the above claim(s) *1,2,4-6,17-46 and 52-60* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3,7-16,47-51 and 61-63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/7/04, 12/10/4*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

An amendment was received and entered on 9/17/07. Applicant's election with traverse of Group 1, claims 3, 7-16, and 47-51 and SEQ ID NOS: 12-16 is acknowledged. Traversal is on the grounds that the restriction unduly limits the scope of the subject matter Applicant regards as the invention. Applicant argues that because one group embraces sequences with "one or more" immunostimulatory sequences, whereas the other group requires 2 immunostimulatory sequences, that there is no undue burden in searching both groups. Applicant also argues that the groups are classified similarly. This is unpersuasive because, while searches for the two groups could overlap, they are non-coextensive. Groups 1 requires only a single immunostimulatory motif, whereas group 2 requires two. The fact that the inventions have the same classification does not mean that the searches are coextensive, or that there is no added examination burden in considering both groups. Nonetheless, claims 61-63 are rejoined because they do not explicitly require two immunostimulatory motifs, and because, in group 1, the second sequence capable of binding a target can be an immunostimulatory motif. The restriction is considered proper and is therefore made FINAL. Rejoinder of restricted subject matter may be considered after identification of allowable claims.

Claims 1, 2, 4-6, and 17-46 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 1/24/07.

Claims 52-60 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 9/17/07.

Claims 1-63 are pending.

Claims 3, 7-16, 47-51, and 61-63, and SEQ ID NOS: 12-16, are under consideration in this Office Action.

Claim Objections

Claim 11 is objected to because it contains the undefined acronyms PSMA, BTLA, TIM-3 and BAFF. Applicant should amend the first claim containing a given acronym to contain the full name of what is implied by the acronym, followed by the acronym in parenthesis.

Specification

The specification is objected to because the brief description of Fig. 10 refers to Fig. 11B instead of Fig. 10B. See paragraph 28 at page 8.

The amendment filed 9/17/07 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: Provisional Application 60/523,935 was added to the priority claim and incorporated by reference. However,

this incorporation by reference constitutes new matter because 60/523,935 was not incorporated by reference in the instant application as filed.

Applicant is required to cancel the new matter in the reply to this Office Action.

Compliance with Sequence Rules

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the following reason(s). Applicant's attention is directed to the final rule making notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998). **The specification at paragraph 249 (Table 2) on page 72, and Figs. 17B and 20, discloses nucleotide sequences in excess of 9 bases that are not accompanied by a SEQ ID NO.** If these sequences are listed in the current Sequence Listing, then the specification should be amended to include the appropriate SEQ ID NO in each of the passages referred to above. If these sequences are not in the current Sequence Listing, then Applicant must provide:

A substitute computer readable form (CRF) copy of the "Sequence Listing".

A substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

To Download Patentin Software, visit http://www.uspto.gov/web/patents/software.htm

For questions regarding compliance to these requirements, please contact:

- For Rules Interpretation, call (571) 272-0951
- For Patentin Software Program Help, call Patent EBC at 1-866-217-9197 or directly at 703-305-3028 / 703-308-6845 between the hours of 6 a.m. and 12 midnight, Monday through Friday, EST.
- Send e-mail correspondence for Patentin Software Program Help @ ebc@uspto.gov.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7, 8, 9 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 7 is drawn to the genus of aptamers that comprise two target binding sequences. The claim requires:

1) that the first target, upon binding the first target binding sequence, does not stimulate an immune response; and that

2) the second target, upon binding the second target binding sequence, does stimulate an immune response.

So, two subgenuses of targets are recited. The first subgenus is the group of targets, that after binding a non-self molecule (an aptamer) will not stimulate an immune response. A review of the pertinent art shows that aptamers in general are considered to be nonimmunogenic (Que-Gewirth et al (Gene Therapy, (2007 Feb) Vol. 14, No. 4, pp. 283-91), Pestourie et al (Biochimie, (2005 Sep-Oct) Vol. 87, No. 9-10, pp. 921-30), and Joshi et al (Current Drug Targets. Infectious disorders, (2003 Dec) Vol. 3, No. 4, pp. 383-400), so this genus is considered to be adequately described.

The second subgenus is the group of targets that, upon binding the second target sequence, does stimulate an immune response. The specification describes CpG-containing aptamers that should be bound by toll-like receptor (tlr) 9, leading to an immune response. Also, the prior art taught that double stranded RNAs were bound by tlr3, leading to an immune response. The specification also teaches that aptamers can be generated which contain sequences other than CpG motifs which are bound by toll-like receptors and stimulate an immune response upon binding. However, none of these sequences is disclosed. Further, no targets, other than tlr3 and tlr9, are disclosed

that stimulate an immune response when bound by a nucleic acid sequence. See paragraphs 164-171.

The written description requirement for genus claims can be met by disclosing a representative number of species by reduction to practice, or disclosing relevant identifying characteristics of the genus, such as a correlation between structure and function. The specification fails to describe immunostimulatory nucleic acid sequences and targets, other than CpG motifs and tlr9 receptors, that when bound by each other stimulate an immune response. The prior art recognized that dsRNAs were bound by tlr9 receptors to stimulate an immune response. However, there is no evidence of record that any other tlr binds nucleic acids and stimulates an immune response, and the specification does not identify any non-tlr9 target that binds a nucleic acid and stimulates an immune response. Accordingly, one of skill in the art could not conclude that Applicant was in possession of targets other than tlr3 or tlr9 that, when bound by a nucleic acid sequence, stimulate an immune response.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States

only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 3, 7-16, 48-51, 61, and 62 are rejected under 35 U.S.C. 102(b) as being anticipated by Janjic et al (US 6,229,002).

Janjic taught ligand 36t (SEQ ID NO: 84) which is identical to instant ARC124 (see table 6 at column 51). This aptamer contains CpG islands and is inherently immunostimulatory as evidenced by the fact that it stimulates release of IL-6 from mouse macrophage cells (see instant Fig. 21C). So, Janjic taught an aptamer that:

a) comprises a first sequence that binds a first ligand (PDGF), wherein there is no evidence of an immune response induced by the resulting complex, without causing an immune response, and

b) comprises a CpG island that is apparently immunostimulatory in view of the results disclosed in instant Fig. 21C. This sequence is considered to have the inherent characteristic of binding toll-like receptors

Janjic also taught a composition comprising the disclosed aptamers and an antitumor drug such as daunorubicin (see column 25, lines 26-32).

Janjic also taught that the aptamers of the invention could contain nonimmunogenic high molecular weight compounds such as polyethylene glycol of molecular weight from 20-45 kDa (see column 15, lines 19-42, and column 26, lines 50-61). Janjic exemplifies 40kDa PEG at e.g. Fig. 9. Thus Janjic anticipates the claims.

Claims 3, 7-10, 13, 48, and 61-63 are rejected under 35 U.S.C. 102(e) as being anticipated by Gorenstein et al (US 20040265912).

The portions of US 20040265912 relied upon in this rejection are supported in the priority document, US Provisional Application 60/472,890, filed 5/23/03. It is noted that the instant application claims priority to US applications 10/718,833, 60/428,102, 60/469,628, 60/464,239, and 60/465,053, but none of these documents provides support for the immunostimulatory sequences embraced by the instant claims. Accordingly the effective filing dates of the instant claims are later than 5/23/03, and US 20040265912 is available as prior art.

Gorenstein taught a pharmaceutical composition comprising concatenated thioaptamers directed against nuclear regulatory factors, wherein the aptamers also comprise a pathogen-associated molecular pattern antigen such as a CpG molecule. See paragraphs 26, 27, 32, and 60. The aptamers may be coupled to biodegradable, bioacceptable polymers such as polyvinylpyrrolidone (see paragraph 64). Thus Gorenstein anticipates the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 3, 9, 10, and 47 rejected under 35 U.S.C. 103(a) as being unpatentable over Gorenstein et al (US 20040265912) in view of any one of Raz et al (US 6,514,948), Carson et al (USD 6,610,661), or Schwartz (US 6,562,798).

The portions of US 20040265912 relied upon in this rejection are supported in the priority document, US Provisional Application 60/472,890, filed 5/23/03. It is noted that the instant application claims priority to US applications 10/718,833, 60/428,102, 60/469,628, 60/464,239, and 60/465,053, but none of these documents provides support for the immunostimulatory sequences embraced by the instant claims. Accordingly the effective filing dates of the instant claims are later than 5/23/03, and US 20040265912 is available as prior art.

Gorenstein taught a pharmaceutical composition comprising concatenated thioaptamers directed against nuclear regulatory factors, wherein the aptamers also comprise a pathogen-associated molecular pattern antigen such as a CpG molecule. See paragraphs 26, 27, 32, and 60.

Gorenstein did not exemplify any specific immunostimulatory CpG molecule.

Raz disclosed SEQ ID NO:12 as an immunostimulatory sequence. See e.g. column 10, lines 12-16.

Carson disclosed SEQ ID NO:12 as an immunostimulatory sequence. See e.g. claims 7, 44, and 55.

Schwartz disclosed SEQ I DNO: 12 as an immunostimulatory sequence. See e.g. Table 1 at column 25.

It would have been obvious to one of ordinary skill in the art at the time of the invention to select any known CpG immunostimulatory sequence to use in the inventions of Gorenstein. Absent evidence of some unexpected result, selection of a sequence is simply a matter of choosing between obvious, equivalent alternatives. It is

clear form the art cited above, that SEQ ID NO: 12 was well known in the prior art as a CpG-containing immunostimulatory molecule, and so it would have been obvious to use it, or any other well known CpG molecule in the invention of Gorenstein.

Claims 3, 9, and 48-51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gorenstein et al (US 20040265912) in view of Janjic et al (US 6,229,002).

Gorenstein taught a pharmaceutical composition comprising concatenated thioaptamers directed against nuclear regulatory factors, wherein the aptamers also comprise a pathogen-associated molecular pattern antigen such as a CpG molecule. See paragraphs 26, 27, 32, and 60. The aptamers may be coupled to biodegradable, bioacceptable polymers such as polyvinylpyrrolidone (see paragraph 64).

Gorenstein did not teach coupling of aptamers to polyethylene glycol.

Janjic taught that the pharmacokinetic properties of aptamers could be improved by conjugation of high molecular weight compounds such as polyethylene glycol of molecular weight from 20-45 kDa (see column 15, lines 19-42, and column 26, lines 50-61). Janjic exemplifies 40kDa PEG at e.g. Fig. 9.

It would have been obvious to one of ordinary skill in the art at the time of the invention to attach PEG of any molecular weight in the range of 20-45 kDa to the aptamers of Gorenstein in order to obtain improved pharmacokinetic properties as taught by Janjic. In particular, Janjic exemplified 40 kDa PEG.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, J. Douglas Schultz, can be reached at (571) 272-0763. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Richard Schnizer, Ph.D.
Primary Examiner
Art Unit 1635